

14 Women with an increased risk of malignancy or previous malignancy

At a glance

- ▶ There is little evidence that hormone replacement therapy (HRT) further increases the risk of breast cancer in women with a family history.
- ▶ Women with a significant family history should be referred to a specialist clinic to determine their individual risk.
- ▶ Vasomotor symptoms are common and often a consequence of breast cancer treatment.
- ▶ Systemic HRT is usually avoided in women with estrogen receptor-positive tumours.
- ▶ Clonidine, citalopram, venlafaxine or gabapentin may be useful for vasomotor symptoms.
- ▶ Herbal treatments are not recommended for breast cancer patients.
- ▶ Lubricants and moisturisers may be prescribed for urogenital atrophy and low-dose vaginal estrogens in the recommended dosage may be used in most women.
- ▶ Tamoxifen increases bone mineral density in postmenopausal but not premenopausal women.
- ▶ Aromatase inhibitors increase bone loss and may induce osteoporosis. All women starting aromatase inhibitors should be assessed for osteoporosis risk.
- ▶ Weight-bearing exercise, calcium and vitamin D should be encouraged and bisphosphonates considered if osteoporosis is already present.
- ▶ Non-hormonal contraception is first-line therapy for breast cancer survivors.
- ▶ Progestogen-only contraception, including the intrauterine system, may be considered in close collaboration with the oncologist.
- ▶ Ovarian (excluding endometrioid), cervical, vaginal and vulval cancers are not estrogen dependent and HRT may be safely prescribed.

- ▶ Treatment for childhood cancers often causes early or premature ovarian insufficiency.
- ▶ Young women with early or premature ovarian insufficiency should have HRT at least until the age of natural menopause.

Women who have had a previous cancer or who are at an increased risk of developing cancer may be reluctant to consider estrogen replacement. However, most cancers are not hormone dependent and so, in most cases, estrogen is not contraindicated. The cancers in which estrogen replacement may have an impact are breast, some gynaecological and colorectal cancers and malignant melanoma. Women who have had previous treatment for cancer in childhood or adolescence may well have developed premature ovarian insufficiency and thus have much to benefit from estrogen replacement.

Breast cancer

Breast cancer is the most common female malignancy, with almost 53,400 new cases being diagnosed in women in the UK in 2013. Although one in eight women in the UK will be diagnosed with breast cancer in their lifetime, the corollary is that seven in eight women will never be diagnosed. Age-specific diagnosis rates begin to rise in women in their 30s but most breast cancers (around 80%) are diagnosed in women over the age of 50 years. Variations in diagnosis rates in postmenopausal women largely reflect eligibility for participation in the National Health Service Breast Screening Programme, as there is an increased risk of diagnosis in the 66–69 years age group. Across all ages, UK deaths from breast cancer have fallen over the last 40 years by nearly 40% and survival continues to improve. Currently, nearly eight in ten women diagnosed with breast cancer will, with optimal treatment, survive their disease for at least ten years and two in three will survive their disease beyond 20 years.

Risk factors for breast cancer

The aetiology of breast cancer is complex and its development is associated with poorly understood relationships between genetic, reproductive and lifestyle factors. Risk factors can be categorised into those that cannot be modified and those that can. Non-modifiable risk factors determine a woman's individual baseline (or absolute) risk. Most

people diagnosed with breast cancer are at population risk, the greatest influence on this being increasing age and female gender. Only a minority of the population have a higher than population risk, due to either an inherited genetic mutation or a biopsy-proven high-risk breast lesion.

Family history of breast cancer

The development of any breast cancer requires mutations of the DNA repair genes. For women who are at the normal population risk and are diagnosed with breast cancer (sporadic breast cancer), these mutations are acquired during their lifetime, due to the effect of carcinogens. Women with a strong familial predisposition have inherited high-risk susceptibility gene mutations (such as *BRCA1* and *BRCA2* mutation carriers). In the UK, only about 2% of cancers diagnosed annually can be attributed to such inherited mutations.

Women with a first-degree relative affected by breast cancer have an increased risk of being diagnosed compared with women with no affected first-degree relatives. High familial risk is associated with a larger number of affected relatives, a history of bilateral breast cancer and a younger age at diagnosis in affected relatives (under 50 years). Most women (around 85%) with an affected first-degree relative will, however, never be diagnosed with breast cancer in their lifetime and 87% of women diagnosed with breast cancer have no first-degree relatives with the disease.

Benign breast disease

The classification of benign breast conditions is histological, with categorisation according to the estimated risk of subsequent breast cancer diagnosis. As most benign breast conditions do not increase a woman's future risk of diagnosis (for example, cysts or fibroadenoma), once a histological diagnosis is confirmed, regular follow-up or surveillance is not indicated. There are two distinct lesions (epithelial atypia and lobular carcinoma in situ) that are associated with a significant increased future risk (relative risk > 4). Both are currently considered to be markers of risk rather than premalignant lesions and are managed by annual mammographic surveillance.

Lifestyle and reproductive risk factors

Lifestyle and reproductive risk factors can be modified and their association with either an increase or a decrease in the risk of breast cancer diagnosis is postulated to be mediated via changes in female sex

hormone exposure or an influence on the differentiation of breast epithelium. The latter is attributed to a greater proportion of less-differentiated cells, which are more susceptible to carcinogens, which explains why increased risk is associated with nulliparity, late age at first full-term pregnancy and not breastfeeding.

Overall lifestyle and reproductive risk factors, including hormone replacement therapy (HRT), confer a similar and small degree of increased risk (risk ratio <2–3). The impact of any modifiable factor is determined by individual baseline risk; the greater this is, the greater the impact of a modifiable risk factor. Most women diagnosed with breast cancer have no known risk factors other than growing older and, conversely, most women with exposure to known lifestyle risk factors are never diagnosed with breast cancer.

Clinical studies, of varying (and often low) quality, evaluating the impact of HRT in women with an elevated baseline risk due to a family history of breast cancer or with a personal diagnosis of a benign breast condition have not shown it to have an additive impact on risk. That is, the degree of estimated risk is the same as that in women at population risk. It therefore follows, for example, that if a woman's baseline risk is elevated owing to her family history or biopsy-confirmed diagnosis of a high-risk benign breast condition, use of HRT is associated with a greater absolute risk compared with women exposed to HRT who are at population risk. In *BRCA* mutation carriers, taking add-back unopposed or combined HRT for amelioration of estrogen deficiency symptoms after prophylactic oophorectomy has not been reported to increase breast cancer diagnosis. Currently, it is recommended in these women that HRT is taken until the age of the natural menopause.

Previous breast cancer

Women treated for breast cancer are at risk of developing acute and longer-term iatrogenic health problems related to estrogen deficiency, as most treatments involve either suppression of estrogen synthesis or antagonism of estrogen activity (for example, chemotherapy, aromatase inhibitors, tamoxifen, luteinising hormone-releasing hormone analogues). Iatrogenic vasomotor symptoms appear to be more severe and longer-lasting than those arising from natural menopause.

Management of menopausal symptoms

National Institute for Health and Care Excellence (NICE) guidance states that women with or at high risk of breast cancer should be offered

information on all the treatment options and should, if necessary, be referred to a health professional with expertise in managing the menopause. General advice such as stopping smoking, limiting alcohol intake, losing weight and increasing exercise may all help to reduce menopausal symptoms and improve quality of life.

The pharmacological alternatives for managing vasomotor symptoms include clonidine, selective serotonin-reuptake inhibitors (citalopram and sertraline) serotonin and norepinephrine reuptake inhibitors (venlafaxine) and gabapentin (see Chapter 9). However, efficacy of these preparations has only been demonstrated in short-term (up to 12 weeks) studies. Desvenlafaxine 100mg daily, which is a serotonin and norepinephrine reuptake inhibitor, has been shown to be more effective than placebo for the treatment of hot flushes in breast cancer survivors. This drug is not available in the UK. Paroxetine and fluoxetine should be avoided in women taking tamoxifen because of their inhibiting effect on the conversion of tamoxifen to its active metabolite. Progestogens such as megestrol acetate and medroxyprogesterone may be helpful but, in effective doses, they can cause weight gain and there are concerns about safety, as high-dose progestogens carry the same risk of venous thromboembolic disease as estrogens and many tumours may also be progesterone sensitive.

Psychological and emotional symptoms which often occur in women going through the menopause and include anxiety, low mood, irritability, poor concentration and loss of self-esteem, may be more pronounced in women who have recently undergone treatment for breast cancer. NICE recommends the use of cognitive behaviour therapy to alleviate low mood and anxiety, which is supported by moderate-quality evidence. Fatigue affects about 20% of women and may persist for many years. There are no well-established management strategies but yoga, acupuncture and relaxation techniques may be helpful. Lifestyle interventions may also be useful for women for whom estrogen therapy is unwanted or contraindicated. The safety and efficacy of alternative and complementary therapies are unknown. Some herbal preparations may contain estrogenic compounds so caution should be advised in women with hormone-responsive disease.

For urogenital symptoms, water-based lubricants and bioadhesive moisturisers may help (see Chapter 6). Low-dose vaginal estrogens may be considered if quality of life is significantly affected, as systemic absorption with these preparations is minimal. NICE recommends that even for women for whom systemic estrogen is contraindicated, vaginal estrogens in the recommended doses may be used after seeking advice from a healthcare professional with expertise in menopause.

Systemic estrogen-based HRT is generally contraindicated in breast cancer survivors, because of concern that it will promote disease

recurrence. It can be hypothesised that HRT may be safe in women with estrogen receptor-negative disease or those with estrogen receptor-positive cancer who are also taking tamoxifen (which has a very strong estrogen receptor binding affinity, thereby antagonising any potential breast stimulatory effect of HRT). In women with a personal history of breast cancer, low-quality observational evidence has not reported an increased risk of recurrence and data from prematurely curtailed randomised trials of HRT are inconsistent, with an increased risk or no impact on risk of recurrence being reported (no mortality increase has been reported). The NICE menopause guidance recognises that some patients experiencing severe vasomotor symptoms refractory to non-hormonal alternatives may request HRT and states it can be prescribed as long as informed consent is obtained and documented after associated risks and uncertainty have been explained. Any decision to prescribe HRT should involve discussion with the patient's specialist breast team.

Conserving the skeleton

Chemotherapy-induced premature ovarian failure increases the risk of subsequent osteoporosis and vertebral fracture. Tamoxifen, as an adjuvant therapy for breast cancer, increases spine and hip bone mineral density in postmenopausal (but not premenopausal women) but does not appear to reverse the deleterious impact of chemotherapy on bone density. However, other adjuvant regimens, such as gonadotrophin-releasing hormone analogues or aromatase inhibitors (anastrozole and letrozole), increase bone loss and induce osteoporosis, increasing the risk of fracture. Bone density should be assessed in premenopausal women where treatments have caused temporary or permanent ovarian suppression and those with estrogen-positive cancers who are taking tamoxifen. It is recommended all women commenced on aromatase inhibitors have assessment of their bone density. The need for and frequency of subsequent dual-energy x-ray absorptiometry should be individualised, depending on estimated future risk in the context of breast cancer treatment. It is advised that breast cancer patients exercise regularly and take calcium and vitamin D supplements. Those with existing osteopenia and osteoporosis should be evaluated for conditions that further deteriorate skeletal health, such as vitamin D deficiency or hypo- and hyperthyroidism. In the absence of metabolic bone disease, bisphosphonates should be considered in women with osteoporosis, and should probably be administered as long as aromatase inhibitor therapy is continued. Bisphosphonates reduce the risk of systemic recurrence and improve breast cancer mortality in postmenopausal women with early-stage breast

cancer, irrespective of estrogen receptor status and other differences in tumour phenotype. Consensus is now growing for the routine use of bisphosphonates as part of systemic adjuvant therapy in all postmenopausal women with early-stage disease.

Cardiovascular disease risk

Circulatory disorders are an important cause of death in breast cancer survivors, especially in the elderly. Left ventricular dysfunction and heart failure are recognised complications of breast cancer treatments. Radiotherapy (particularly left-sided) has been associated with an increased risk of pericardial disease, cardiomyopathy, valvular dysfunction and arrhythmias, and an increased long-term risk of death from cardiovascular events. However, much of this evidence involved older radiation techniques and higher doses than are now used in clinical practice. Anthracycline-based, polychemotherapy regimens are associated with a 10% mean reduction in left ventricular function compared with pretreatment values. A 14% absolute increase in risk of heart failure and cardiomyopathy is estimated to occur with exposure to trastuzumab, especially in older women. Tamoxifen is not associated with an increased risk of cardiovascular events but there is a small increased risk of diagnosis of venous thromboembolism and cerebrovascular events (two- to three-fold) in postmenopausal women. Aromatase inhibitors, however, are associated with a small increased risk of cardiovascular events. Presently, there is no agreed guidance for cardiovascular health in breast cancer patients apart from regular echocardiography monitoring during trastuzumab therapy.

Fertility

Improving survival rates after diagnosis and treatment for breast cancer means that fertility and contraception are now important survivorship issues. Women are usually advised to avoid becoming pregnant when they are receiving adjuvant systemic therapies, as their effect on the developing fetus are unknown, and not to conceive within two years of diagnosis, as there is a higher risk of cancer recurrence. Pregnancy after breast cancer diagnosis and treatment has not been shown to adversely affect survival but an effect of selection bias cannot be excluded, as it is more likely women with better prognosis disease elect to become pregnant.

Fertility will be impacted by breast cancer treatment that induces ovarian suppression. Chemotherapy does suppress ovarian activity and

Table 14.1

The risk of permanent amenorrhoea with various chemotherapy agents (Lambertini et al., 2016)

Risk of permanent amenorrhoea	Adjuvant regimen
High (>80%)	Cyclophosphamide-based polychemotherapy in women ≥ 40 years
Intermediate (40–60%)	Cyclophosphamide-based polychemotherapy in women 30–39 years Anthracycline-based polychemotherapy in women ≥ 40 years
Low (<20%)	Cyclophosphamide-based polychemotherapy in women ≤ 30 years Anthracycline-based polychemotherapy in women <40 years
Unknown	Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)

the risk of permanent amenorrhoea developing is dependent on increasing age (owing to ovarian follicle depletion) and the chemotherapy regimen used (the risk is greater with alkylating agents such as cyclophosphamide; Table 14.1).

Fertility treatments such as oocyte and embryo cryopreservation may not be possible for some women because of the timing of their chemotherapy. Gonadotrophin-hormone releasing hormone agonists may protect against chemotherapy-induced ovarian failure, although the mechanisms underlying this are not fully understood. Clinical trials have reported a reduced risk of chemotherapy-induced ovarian failure and increased pregnancy rates, without any obvious negative impact on prognosis. Current guidelines only recommend the use of luteinising hormone-releasing hormone agonists in women with estrogen receptor-positive breast cancer, owing to safety concerns. This is based on prior evidence showing attenuation of chemotherapy benefit with the concurrent use of tamoxifen and increased survival of women with estrogen receptor-positive cancer who developed chemotherapy-induced amenorrhoea.

Contraception

Hormonal contraception is not recommended in pre- or perimenopausal women with breast cancer. It is probably safe in those with estrogen

receptor-negative breast cancer but there is a complete lack of any clinical trial evidence to support this. Likewise, there are no clinical data about the use of the 'morning-after' pill but it is unlikely that a single dose of levonorgestrel or a progesterone receptor modulator will have any significant impact. The Faculty of Sexual and Reproductive Healthcare does not advise the use of any hormonal contraception in patients currently undergoing treatment for breast cancer (*UK Medical Eligibility Criteria for Contraceptive Use* category 4: a condition which represents an unacceptable health risk if the method is used).¹ Hormonal contraception is not recommended for women no longer receiving treatment for their breast cancer, as the theoretical risks are considered to outweigh the benefits (UKMEC category 3: a condition where the theoretical or proven risks usually outweigh the advantages of using the method).¹ Despite the UKMEC guidance differentiating between current and past breast cancer in clinical practice, women are usually advised to use barrier methods or the intrauterine contraceptive device. In those not on any breast cancer treatment, where non-hormonal methods are unacceptable, use of hormonal contraception should involve discussion with the woman's oncologist. In the absence of any clinical data in breast cancer survivors, it would be prudent to avoid injectable or implant-based preparations that cannot be 'stopped' in the event of the diagnosis of recurrence. The use of the intrauterine system is also best avoided, although it can at least be removed in the event of a recurrence. There are no reliable data that the intrauterine system is safe, although one small study did not find any evidence of an increased risk of recurrence.

Gynaecological cancers

Ovarian, cervical, vaginal and vulval cancers are not estrogen-dependent conditions, so estrogen replacement is not contraindicated. Non-hormonal therapies for osteoporosis or menopausal symptoms can also safely be used if indicated. The safety of complementary and alternative medicines, such as botanicals, is unknown.

Ovarian cancer

Studies of estrogen replacement in women with ovarian cancer have not shown any detrimental effect on survival, although they have been mainly observational. There are very limited data regarding endometrioid ovarian cancer. Given its potential estrogen dependence, the use of combined estrogen and progestogen HRT rather than estrogen alone

seems prudent, on the premise that the progestogen will suppress any estrogen-stimulated growth. However, there is no strong scientific evidence to support this practice.

BRCA1 and BRCA2 mutation carriers

Mutations such as *BRCA1* and *BRCA2* increase the risk of ovarian cancer. The average cumulative lifetime risk has been estimated to be as high as 60% for *BRCA1* and 40% for *BRCA2* mutation carriers. Bilateral prophylactic oophorectomy is increasingly being performed in these women, leading to premature ovarian insufficiency in those who are premenopausal. Data regarding HRT use in *BRCA* gene carriers are still fairly limited but show no adverse effect, and HRT is usually recommended at least until the age of 50 years.

Endometrial cancer

Endometrial cancer is the fourth most common female cancer in the UK with an incidence of 13/100,000 and a mortality of approximately 2/100,000. The incidence is rising owing, at least in part, to an increase in obesity. The relatively few published studies on the use of HRT in women with a history of endometrial cancer do not show any increase in recurrence or death rate among HRT users; thus, its use in endometrial cancer survivors does not seem to be contraindicated. However, the studies are limited by small sample size, retrospective design, selection bias, variation in hormone preparations and disease severity. Therefore, although the available data are encouraging, the question of whether or not HRT should be given after endometrial cancer remains contentious. The American College of Obstetricians and Gynecologists has stated that there is insufficient evidence to support specific recommendations of the use of HRT in women with a history of endometrial cancer.² They have commented that, although the indications for use of HRT in this population are similar to those for other women, women should be selected on the basis of prognostic indicators, such as depth of invasion, grading and cell type, and the risk the woman is willing to take. A woman with stage 1A cancer treated surgically has a recurrence risk of less than 2% and topical estrogens may be considered if indicated. Women with surgically treated cancer could consider starting systemic HRT if symptoms are severe. Combined HRT may be more appropriate but evidence to support this is limited. Women who do not wish to take HRT should be advised about osteoporosis protection.

Cervical cancer

Cervical cancer is not an estrogen-dependent disease and thus HRT is not contraindicated. In women who have had a hysterectomy, estrogen only can be used. However, in those treated by chemoradiotherapy and in whom the uterus is retained, it cannot be assumed that all the endometrium has been destroyed. Indeed, there are reports of persisting functioning endometrial tissue and cancer after definitive radiation treatment for invasive cervical cancer. Therefore, women who retain their uterus must have combined HRT. Moreover, ovarian activity may return and an effective form of contraception needs to be advised, since the outcomes of pregnancy in this situation are unknown. Cervical intraepithelial neoplasia or the presence of human papillomavirus are not contraindications to estrogen use.

Other cancers

Colorectal cancer

Women are less susceptible to colorectal cancer and benign colonic adenomas than men. Large-scale, randomised and observational studies have consistently shown that HRT users have a reduced risk of colorectal cancer, although the mechanism for this is unclear. There are no data on the use of HRT in women at increased risk of the disease or with previous cancer but there is nothing to suggest that it should have any detrimental effect.

Malignant melanoma

While it is generally accepted that there is no direct association between the risk of melanoma and the use of HRT, there have been some contradictory reports of a relation between the prognosis of melanoma and HRT use. Estrogen receptors are present in melanomas but it seems unlikely that estradiol has a direct effect on melanogenesis. Lentigo maligna, which are the precursors of lentigo maligna melanoma, possess both estrogen and progesterone receptors, suggesting a possible role of these steroids in malignant transformation. However data from the Women's Health Initiative study published in 2011 looking at rates of melanoma and non-melanoma skin cancers found that HRT did not affect the incidence of any type of skin cancer.³

Childhood cancers

Approximately 70% of children and adolescents diagnosed with cancer will survive into adulthood. Many women survivors will have premature ovarian failure following cancer treatments. Not all girls receiving radiotherapy or chemotherapy will lose all their ovarian function; however, even those who continue to menstruate appear to be at increased risk of premature menopause. This leads to loss of fertility and increased risks of osteoporosis and cardiovascular disease. An American study from 2006 found that the incidence of premature menopause in childhood cancer survivors treated with chemotherapy and radiotherapy was 30%.⁴ A 2013 French study of 1000 women survivors of childhood cancer treated between 1945 and 1985 found that the incidence of premature menopause in this group was less common, with a median age of menopause of 44 years.⁵ This is still earlier than the general population but menopause under 40 years was uncommon. The highest risk ratio for non-surgical menopause was in women treated after puberty with alkylating agents (risk ratio 29, 95% confidence interval 8–108, $P < 0.0001$). The risk of an early menopause was greatest if the ovaries were irradiated. Both these studies relied on self-reporting and no hormone assays were carried out to confirm menopausal status.

Newer therapies use high doses of alkylating treatments and so an even higher rate of early and premature menopause can potentially be expected. Fertility preservation for these young women with oocyte cryopreservation is an evolving science showing encouraging results. These young women with early or premature menopause will need estrogen replacement to help them to maintain sexual function, to conserve bone density and to protect the cardiovascular system. Contraceptive needs must also be addressed, as spontaneous recovery of ovarian function can occur, leading to a potential pregnancy risk.

References

- 1 Faculty of Sexual and Reproductive Healthcare. *UK Medical Eligibility Criteria for Contraceptive Use*. London: FSRH; 2016.
- 2 Committee on Gynecologic Practice. ACOG committee opinion. Hormone replacement therapy in women treated for endometrial cancer. Number 234, May 2000 (replaces number 126, August 1993). *Int J Gynaecol Obstet*, 2001; 73: 283–4.
- 3 Tang JY, Spaunhurst KM, Chlebowski RT, Wactawski-Wende J, Keiser E, Thomas F, et al. Menopausal hormone therapy and risks of melanoma and non melanoma skin cancers. WHI randomized trials. *J Natl Cancer Inst*, 2011; 103(19): 1469–75.

- 4 Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survival study. *JNCI J Natl Cancer Inst*, 2006; 98(13): 890–6.
- 5 Cecile Thomas-Teinturier et al. Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: earlier but not premature. *Hum Reprod*, 2013; 28(2): 488–95.

Further reading

Breast cancer

- Hadji P, Coleman RE, Wilson C, Powles TJ, Clézardin P, Aapro M, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Ann Oncol*, 2016; 27(3): 379–90.
- Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA Jr, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med*, 2016; 14: 1. doi: 10.1186/s12916-015-0545-7.
- Lambertini M Ceppi M, Poggio F, Gamucci T, Scotto T, Gori S, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. *JAMA*, 2015; 314(24): 2632–40.
- Maas AH Ottevang N, Atsma F, Cramer MJ, Leiner T, Poortmans P. Cardiovascular surveillance in breast cancer treatment: a more individualized approach is needed. *Maturitas*, 2016; 89: 58–62.
- Marsden J. The menopause specialist and breast cancer survivorship. *Post Reprod Health*, 2016; 22(4): 147–54.
- Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. *Nat Rev Clin Oncol*, 2015; 12: 227–38.
- National Institute for Health and Care Excellence. *Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People with a Family History of Breast Cancer* (Clinical Guideline CG164). London: NICE; 2013.

Gynaecological cancer

- Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS, Gynecologic Oncology Group Study. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*, 2006; 24: 587–92.
- Bebar S, Ursic-Vrscaj M. Hormone replacement therapy after epithelial ovarian cancer treatment. *Eur J Gynaecol Oncol*, 2000; 21: 192–6.
- Guidozzi F. Hormone therapy in gynaecological cancer survivors. *Climacteric*, 2013; 16: 611–17.

- Kotsopoulos J, Lubinski J, Neuhausen SL, et al. Hormone replacement therapy and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. *Gynecol Oncol*, 2006; 100: 83–8.
- Mascarenhas C, Lambe M, Bellocco R, et al. Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival. *Int J Cancer*, 2006; 119: 2907–15.
- McDonnell BA, Twiggs LB. Hormone replacement therapy in endometrial cancer survivors: new perspectives after the heart and estrogen progestin replacement study and the women's health initiative. *J Low Genit Tract Dis*, 2006; 10: 92–101.
- Ursic-Vrscaj M, Bebar S, Zakelj MP. Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival. *Menopause*, 2001; 8: 70–5.

Other cancers

- Barzi A, Lenz AM, Labonte MJ, Lenz HJ. Molecular pathways: estrogen pathway in colorectal cancer. *Clin Cancer Res*, 2013; 19(21): 5842–8.
- Foster PA. Oestrogen and colorectal cancer: mechanisms and controversies. *Int J Colorectal Dis*, 2013; 28(6): 737–49.
- Kennelly R, Kavanagh DO, Hogan AM, Winter DC. Oestrogen and the colon: potential mechanisms for cancer prevention. *Lancet Oncol*, 2008; 9: 385–91.
- La Vecchia C, Gallus S, Fernandez E. Hormone replacement therapy and colorectal cancer: an update. *J Br Menopause Soc*, 2005; 11: 166–72.
- Prihartono N, Palmer JR, Louik C, Shapiro S, Rosenberg L. A case–control study of use of post-menopausal female hormone supplements in relation to the risk of large bowel cancer. *Cancer Epidemiol Biomarkers Prev*, 2000; 9: 443–7.

Melanoma

- De Giorgi V, Gori A, Grazzini M, Rossari S, Scarfi F, Corciova S, et al. Estrogens, estrogen receptors and melanoma. *Expert Rev Anticancer Ther*, 2011; 11(5): 739–47.
- Naldi L, Altieri A, Imberti GL, Giordano L, Gallus S, La Vecchia C, Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology (GISED). Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case–control study from Italy. *Ann Epidemiol*, 2005; 15: 545–50.